

### Remarks

Applicants respectfully request favorable reconsideration in view of the following remarks.

### Amendments

Applicants request that claims 16 through 33 be cancelled without prejudice or disclaimer in an effort to expedite prosecution. Claims 1 through 15 were previously cancelled. Applicants respectfully request the addition of new claims 34 through 63.

Support for new claim 34 may be found, for example, in currently cancelled claim 18. Support for new claims 35-46 may be found, for example, in originally filed claim 3. Support for new claim 47 may be found, for example, on page 5 of the originally filed application. Support for new claims 48-50 may be found, for example, in currently cancelled claim 20. Support for new claim 51 may be found, for example, in currently cancelled claim 21. Support for new claim 52 may be found, for example, in currently cancelled claims 20, 21, 22 and originally filed claim 3. Support for new claims 53-56 may be found, for example, in Figure 4 of Patent Application No.180/MAS/2002, to which the present application claims priority. Support for new claims 57 and 58 may be found, for example, in currently cancelled claims 28 and 30. Support for new claims 59-63 may be found, for example, in currently cancelled claims 23-27.

New claim 34 and 35 have also been amended to reflect that the angles of each peak may vary by about  $\pm 0.1$ . One skilled in the art would understand that this variation is inherent in diffractometers, e.g., the Rigaku D/Max model diffractometer disclosed on page 5, lines 22-24 of the application as filed, and may be attributable to slight variations in the disclosed diffraction procedures resulting from machine calibration, settings, etc., and from variations from instrument to instrument and operator to operator. Applicants also note that currently cancelled claim 22 contained a typographical error in Applicants' Response of October 5, 2006. The listing of X-ray diffraction peaks recited in claim 22 in Applicants' Response of October 5, 2006 mistakenly omitted several X-ray diffraction peaks. This typographical error was made without any deceptive intent and should in no way be construed as a disclaimer. Applicants have corrected this typographical error in the listing of new claims, e.g., new claims 34-63.

Applicants submit that the new claims do not introduce new matter. As such, new claims 34 through 63 are pending.

Initially, Applicants would like to clarify that the claimed invention is directed to two crystalline polymorphs of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]-methoxy]benzyl]thiazolidine-2,4-

dione potassium salt. The first crystalline structure is Form, which is the subject of new claim 34. The second crystalline structure is Form-I, which is the subject of new claims 35-63.

Applicants submit, as set forth in the application as filed and as indicated by the reference, that no crystalline form of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]-methoxy]benzyl]thiazolidine-2,4-dione potassium salt was known prior to the present invention, and that no polymorphs of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]-methoxy]benzyl]thiazolidine-2,4-dione potassium salt were known prior to the present invention. Form and Form-I have novel and nonobvious crystalline structures as indicated by their x-ray diffractometry, differential scanning calorimetry, and infra red spectroscopy. Applicants respectfully submit that differences various solid-state forms of a compound, can translate into patentable differences in biological activity and efficacy.

### 35 U.S.C. §102

Claims 16-18, 20-24 and 28-33 were rejected under 35 U.S.C. §102 as allegedly inherently anticipated by Chebiyyam, et al. (WO 00/15638; “Chebiyyam”). Applicants respectfully traverse this rejections. Applicants have currently cancelled claims 16-18, 20-24 and 28-33 in an effort to expedite prosecution and believe the cancellation of these claims renders the Office’s rejections moot. Applicants will, however, address the Office’s rejections to the extent that those rejections apply to the newly added claims in an effort to further expedite prosecution.

In support of its anticipation rejections the Office states (emphasis added by Applicants):

In Example 40, Chebiyyam et al. describes a process of making the potassium salt of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]-methoxy]benzyl]thiazolidine-2,4-dione (or Glitazone).

The disclosed process reads on the process recited in the instant claim 23 with solvent of xylene:MeOH, heating at temperature ~ 80°C, and potassium t-butoxide added. Because the disclosed process is similar to the claimed process, it is presumed that the same crystal (as recited in claims 16-18 and 20-22) would be obtained.

Thus, it appears that the Office’s anticipation rejections of claims directed to crystalline Form and crystalline Form-I are based on a superficial similarity between Chebiyyam’s Example 40 and Applicants’ claim 23, which is directed to a process of making crystalline Form-I. Applicants respectfully submit that “similarity” between a reference and a claimed invention is insufficient to establish anticipation. Applicants believe it is well established that “[a]nticipation requires the presence in a single prior art reference disclosure of every element of the claimed invention.” *Great Northern Corp. v. Davis Core & Pad. Co., Inc.*, 228 U.S.P.Q. 356, 358 (Fed. Cir. 1986).

Currently cancelled claim 23 recites *heating to a temperature of about 60-75°C* and recites *adding potassium tertiary butoxide at a temperature of 40-55°C*. Chebiyyam's Example 40 fails to disclose or suggest either of these limitations. For at least these reasons, Applicants respectfully submit that Chebiyyam does not anticipate currently cancelled claim 23 or newly added claim 59 having similar limitations.

Further, it is well settled that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public." *In re Hoeksema*, 158 USPQ 596, 601 (CCPA 1968). Applicants respectfully submit that because Chebiyyam does not anticipate or suggest the process of currently cancelled claim 23, Chebiyyam cannot be presumed to anticipate the claimed crystalline Form or the claimed crystalline Form-I. For at least this reason, Applicants request favorable reconsideration of new claims.

Applicants also respectfully disagree with the Office's use of Chebiyyam's *single process* of Example 40 to allege anticipation of *both* Form and Form-I. As set forth in the specification and in the claims, crystalline Form and crystalline Form-I are made by difference processes. Applicants do not believe that a single process can be used to anticipate both Form and Form-I, and request favorable reconsideration on these grounds.

Chebiyyam also fails to provide other limitations of the claimed invention. For example, regarding currently cancelled claim 25, Applicants respectfully submit that Chebiyyam's Example 40 fails to disclose, inter alia, the recited *dissolving at room temperature*. Chebiyyam explicitly discloses that dissolving is performed at 80-90°C. For at least this reason, Applicants respectfully submit that Chebiyyam does not anticipate currently cancelled claim 25, or new claims 58-63 having similar limitations.

Applicants also respectfully submit that the Office has not met its burden in alleging *inherency*. In Applicants' Response of October 5, 2007, Applicants emphasized that the Board of Patent Appeals in *Ex parte Havens* did not consider a salt to render a new crystal form inherently anticipated. The Office responded that *Ex parte Havens* "is an unpublished decision, and thus cannot serve as legal precedent." The Board's decision in *Ex Parte Havens* was based on *Ex parte Skinner*, 2 USPQ 2d 1788 (Bd. Pat. App. Int. 1986), which Applicants respectfully submit is legal precedent. In *Ex parte Skinner*, the Board held that **when inherent properties of a prior art product are at issue, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the**

**functional limitation is an inherent characteristic of the prior art” before the burden is shifted to the applicant to disprove inherency. *Id.* at 1789.**

Applicants submit that the Office has failed to provide evidence in support of its inherency rejection because Applicants’ specification and claims show that Form and Form-I are two different crystalline structures. For example, Form is crystalline with x-ray powder diffraction peaks selected from the group consisting of 6.20, 9.34, 12.16, 12.48, 15.06, 18.26, 18.80, 24.02, 24.46, 26.70, 27.02, 27.48, and 30.86. In contrast, Form-I is crystalline with an x-ray powder diffraction pattern comprising peaks selected from the group consisting of 6.44, 7.42, 9.28, 10.76, 11.24, 16.16, 18.60, 25.06, 28.42, and 30.40. Applicants submit that Chebiyyam’s Example 40, which is a single process different from the processes of the claimed invention, cannot inherently produce both Form having one set of x-ray powder diffraction peaks and Form-I having a different set of x-ray powder diffraction peaks. For at least this reason, Applicants respectfully request favorable reconsideration.

Further, based on *Ex parte Skinner*, Applicants respectfully request evidence for each of the claimed limitations that the Office believes are inherent in the product produced by Chebiyyam’s Example 40.

On a related note, Applicants respectfully direct the Office’s attention to numerous decisions, which are also precedential, setting forth that new crystalline forms of old compounds are patentable and are not rendered obvious by old forms of the compound. See for example, *In re Cofer*, 148 USPQ 268 (CCPA 1966); *In re Irani*, 166 USPQ 24 (CCPA 1970); and *In re Grose*, 201 USPQ 57 (CCPA 1979).

### 35 U.S.C. §103

Claims 19 and 25-27 were rejected under 35 U.S.C. §103 as unpatentable over Chebiyyam. Applicants traverse these rejections. Applicants believe that the cancellation of claims 19 and 25-27 renders the Office’s rejections moot, but, Applicants will address the Office’s rejections to the extent that they apply to the new claims.

To establish a prima facie case of obviousness, three basic criteria must be met (MPEP 2143):

- (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- (2) There must be a reasonable expectation of success; and
- (3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

In explaining the basis for its obviousness rejections, the Office states:

The process disclosed in Example 40 of WO'638 differs from the process recited in claim 19 by having the solvent of xylene:MeOH, and not xylene:acetonitrile. The disclosed process also differs from the process recited in claims 25-27 by different temperature range. However, xylene, MeOH and acetonitrile are known organic solvents used [in] many reaction schemes, and thus would be within the level of the skilled chemist to select to achieve desirable yield. Likewise, the difference in temperature range would also be within the level of the skilled chemist to select to obtain optimum yield.

Regarding currently cancelled claim 19, Chebiyyam's example fails to disclose or suggest, inter alia, the recited *adding of potassium tertiary butoxide at room temperature*. Chebiyyam discloses adding at 60-70° C, which represents a difference of approximately 35-45° C. Regarding currently cancelled claim 25, Chebiyyam's example fails to disclose or suggest limitations (i) and (ii). Regarding currently cancelled claim 27, Chebiyyam's example fails to disclose, inter alia, limitation (ii).

The first sentence of the first MPEP paragraph cited by the Office (Optimization Within Prior Art Conditions or Through Routine Experimentation) states: "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art **unless there is evidence indicating such concentration or temperature is critical**"(emphasis added by applicants). In the present case, Applicants' specification shows that the process of manufacturing the crystalline compound is important to achieve the recited crystalline structure of Form or Form-I. Applicants' specification clearly shows that by changing the process, different polymorphs can be achieved. Applicants are not, as suggested by the Office, changing parameters to "obtain optimum yield [in terms of amount]", Applicants are creating completely new solid-state structures, the characteristics of which are not suggested by the reference. For at least these reasons, Applicants respectfully submit that currently cancelled claims 19 and 25-27, and new claims 61-63 having similar limitations, are not rendered obvious by the reference.

Conclusion

Applicants believe that by this amendment the case is placed in condition for allowance and such action is respectfully requested. If, however, any issues remain unresolved, Applicants' representative would welcome the opportunity for a telephone interview to expedite allowance and issue.

Respectfully Submitted,

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Date: July 26, 2007